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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,185	08/07/2006	Hans-Peter Buchstaller	24945-0026US	8027
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BAKER & DANIELS LLP 805 15TH STREET, NW, SUITE 700 WASHINGTON, DC 20005			EXAMINER LOEWE, SUN JAE Y	
			ART UNIT 1626	PAPER NUMBER
			MAIL DATE 10/25/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/564,185	Applicant(s) BUCHSTALLER ET AL.	
	Examiner Sun Jae Y. Loewe	Art Unit 1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 September 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13, 15-24 and 28-31 is/are pending in the application.
- 4a) Of the above claim(s) 12, 13, 15-24 and 28-31 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3 and 5-11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>4/24/2006</u> | 6) <input type="checkbox"/> Other: _____ |

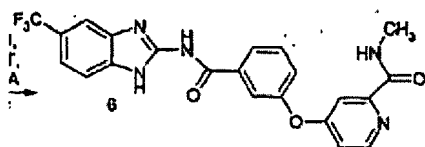
DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I and compound 6,

4-[3-(5-Trifluoromethyl-1H-benzimidazol-2-yl) carbamoyl) phenoxy] pyridine-2-carboxylic acid, methyl amide. (below)

in the reply filed on September 21, 2007 is acknowledged.



The traversal is on the ground(s):

“Applicants traverse the restriction because the search of more than one Group would not place an undue burden on the Examiner.”

This argument is not found persuasive. The search for the full scope of Formula I and Formula II (ie. Groups I and II), *for example*, encompasses structures with the common motif of benzimidazole bound to nitrogen. A sample search for this core structure leads to 38,758 - 44,222 projected answers that must be considered to determine compliance with 35 USC 102 and 35 USC 103 (see exhibit below). The consideration of such large answer set, which is only a portion of the search required for the examination of the full scope of subject matter in Groups I-V (restriction requirement dated July 25, 2007), is deemed to be burdensome.

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l1 sam

SAMPLE SEARCH INITIATED 07:26:04 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 5645 TO ITERATE

35.4% PROCESSED 2006 ITERATIONS 50 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00:00:01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**

BATCH **COMPLETE**

PROJECTED ITERATIONS: 106395 TO 117405

PROJECTED ANSWERS: 39752 TO 46222

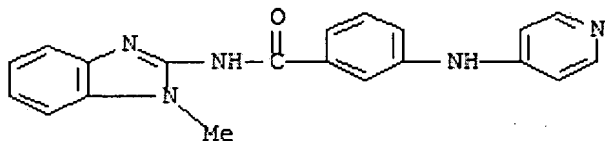
The restriction requirement is still deemed proper and is hereby made FINAL.

2. Claims 4, 12, 13, 15-24 and 28-31 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter.

3. MPEP § 803.02 provides guidelines for election of species in Markush-type claims.

These guidelines were followed for the search and examination detailed herein.

The elected species appeared to be allowable over the art of record, therefore the search and examination was extended to the non-elected species of ($p=q=r=0$; $R^6=A=\text{alkyl}$; $R^7=\text{hydrogen}$; $Y=\text{oxygen}$; $X=(\text{CHR}^{11})_h\text{-Q-(CHR}^{12})_h$ with $h=i=0$ and $Q=N\text{-R}^{15}$ and $R^{15}=\text{hydrogen}$; $\text{Ar}^2=\text{pyridine}$:



which is anticipated by the prior art (below, Section 9). The Markush-type claims were thus rejected and the subject matter drawn to nonelected species held withdrawn from further consideration.

Claims 1-3 and 5-11 were further examined, pursuant to MPEP § 803.02, to the extent necessary to determine patentability. The search was limited to the elected species and the non-elected species identified above.

It has been determined that the entire scope claimed is not patentable.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on April 24, 2006 was in compliance with the provisions of 37 CFR 1.97 and 37 CFR 1.98. The IDS was considered. A signed copy of form 1449 is submitted herewith.

Claim Objections

5. Claims 1-3 and 5-11 objected to for containing non-elected subject matter.

Claim Rejections - 35 USC § 112 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

(Written Description)

6. Claims 1-3 and 6-11 rejected under 35 USC 112 1st paragraph as failing to comply with the written description requirement.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

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“To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that “the inventor invented the claimed invention.” *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (“[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.”). Thus, an applicant complies with the written description requirement “by describing the invention, with all its claimed limitations, not that which makes it obvious,” and by using “such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention.” *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.” *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

“A written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as by structure, formula, [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials.” *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) (“In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...”) *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

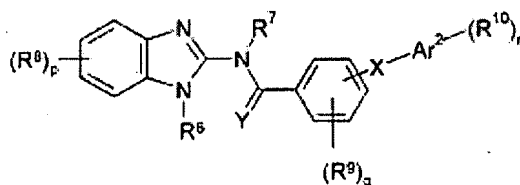
The MPEP states that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad genus. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

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The Guidelines for Examination of Patent Applications Under 35 USC 112, ¶1, "Written Description" Requirement (Federal Register, Vol. 66, No. 4, pg. 1105, column 3), in accordance with MPEP § 2163, specifically state that for each claim drawn to a genus the written description requirement may be satisfied through sufficient description of a representative number of species by a) actual reduction to practice; b) reduction to drawings or structural chemical formulas; c) disclosure of relevant, identifying characteristics (ie. structure) by functional characteristics coupled with a known or disclosed correlation between function and structure. The analysis of whether the specification complies with the written description requirement calls for the examiner to compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention (Federal Register, Vol. 66, No. 4, p. 1105, 3rd column, 3rd paragraph). Below is such comparison.

I. Scope of Claims

Compounds of Formula I



The following variables are claimed broader than what is supported by the disclosure (see below section II):

R ⁶ , Ar ² :	for all claims <u>except</u> 3
X, Y, R ⁷ -R ¹⁰ :	for all claims

II. Scope of Disclosure

Reduction to Practice:

The compounds reduced to practice support the following definitions for the variables noted above.

R ⁶ /R ⁷ :	hydrogen or unsubstituted alkyl, haloalkyl, halogen
R ⁸ /R ⁹ :	hydrogen, unsubstituted alkyl, haloalkyl, halogen
R ¹⁰ :	- hydrogen, unsubstituted alkyl, haloalkyl, halogen,

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- $(CH_2)_nCONR^{11}R^{12}$; wherein R11/R12=hydrogen, unsubstituted alkyl, haloalkyl, halogen

X/Y: oxo
Ar²: pyridinyl

Reduction to Structural or Chemical Formulas:

The only disclosure, in addition to the species reduced to practice, is in form of lists of possible groups (eg., dioxane, 1,3-dioxane, pyrrolidine, piperidine, morpholine, for heterocycle). This type of disclosure is not viewed to be a representation of any of the species it entails. A "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species. MPEP 2163.I.A. and *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996). Therefore, there is no disclosure of species (eg. by reduction to structural/chemical formulas) in addition to those reduced to practice.

Correlation between Structure and Function:

A correlation between structure and function, for the instantly claimed genus of compounds, is neither known in the art nor disclosed in the specification. Thus, it is not understood what specific structural elements are essential for the activity of the instantly claimed compounds as Raf kinase inhibitors.

III. Analysis of Fulfillment of Written Description Requirement:

The structure/activity relationship (SAR) for binding and activity is elucidated upon analysis of IC₅₀ data of multiple compounds with various types of structural modifications. These types of studies provide insight into the structural limitations that are required for activity, ie. specific structural elements essential for the claimed activity. In the absence of such correlation, it is not possible to determine what structural modifications will allow for the preservation of the desired activity.

In conclusion: (i) substantial structural variation exists in the genus/subgenus embraced by claims 1-3 and 6-11; (ii) disclosure of species supporting genus is limited to compounds reduced to practice, which scope is not commensurate with the scope of genus/subgenus claimed; (iii) common structural attributes of the claimed genus/subgenus, combined with a correlation between structure and function, is neither disclosed in the instant application nor commonly known in the art. Thus, the specification fails to provide adequate written description for the genus of compounds claimed and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

(Enablement)

7. Claims 1-3 and 6-11 rejected under 35 U.S.C. 112, first paragraph. The specification is enabling for the use of the compounds that have adequate written description. The specification is not enabling for

- (a) The use of compounds not supported by the disclosure.
- (b) The full scope of intended use recited (ie. "kinase inhibitor."), for the compounds that do have sufficient written description support

In conclusion, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8USPQ2s 1400, 1404 (Fed. Cir. 1988). MPEP 2164.01(a) states "There are many factors to be

considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue". The factors are applied below to the instant claims.

The breadth of the claims

- (a) Compounds not supported by the disclosure (see above section 6.I and 6.II.).
- (b) Compounds are claimed inhibitors of "kinases".

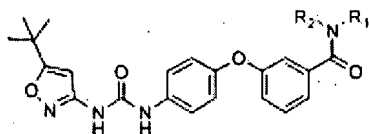
The nature of the invention

- (a) The compounds are disclosed to be kinase inhibitors (instant specification page 1). An alternate utility is neither disclosed in the specification nor known in the art for this genus of compounds.
- (b) "Kinase" is a broad term that encompasses enzymes that transfer phosphate from from donor molecules to specific substrates. This groups of enzymes is highly diverse (structure and function), with up to 518 different kinases identified in humans alone. See <http://en.wikipedia.org/wiki/Kinase>.

The state of the prior art/level of ordinary skill/level of predictability

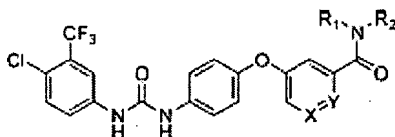
- (a) The level of ordinary skill is high, but the level of predictability in the art is low. Although SAR studies are not available for the instantly claimed genus of compounds, these studies have been disclosed for other compounds that are kinase inhibitors, see example below.


- Khire et al., Table 1:



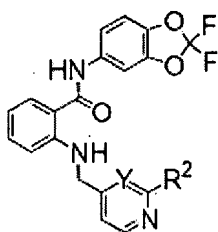
- For example, changing $-NR_1R_2$ from $-NHMe$ to $-NMe_2$ effects 50-fold increase in IC_{50} (nM) for Raf kinase
 - For example, changing $-NR_1R_2$ from $-NHMe$ to $-NH(n-Pr)$ does not noticeably affect IC_{50} (nM) for Raf kinase
- Khire et al., Table 2:

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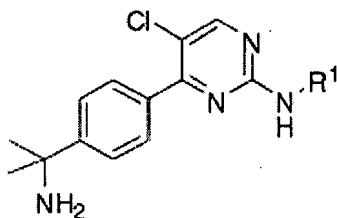
- For example, changing  from pyridinyl to phenyl effects approx 10-fold increase in IC₅₀ (μM) for Raf kinase

- Wickens et al., Table 2:



- For example, changing R² from –NH₂ to NHCOCH₃ effects an approx 100-fold *difference* in the specificity of the compound towards B-Raf (a serine/threonine kinase receptor) as measured against c-KIT (a receptor tyrosine kinase), both of which are considered to be “kinases”.

- Huang et al., Table 1



- Compounds of this core structure displayed selectivity towards inhibiting VEGFR-2 over CDK1, both of which are “kinases”.

As discussed in section 6, it is not known what structural limitations are required for preservation of activity within the genus claimed. In view of the low level of predictability for inhibiting kinases, broadly, as well as specifically a single kinase, one of ordinary skill would not know what structural modifications within the unrepresented genus (ie. unrepresented by the disclosure), if any, would lead to compounds that are active.

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- (b) The level of predictability for inhibiting a single kinase is low. The level of predictability for a single compound to inhibit multiple kinases is also low. See discussion and examples above section (a).

The amount of direction provided by the inventor/existence of working examples

- (a) No direction or working examples.
- (b) The direction/guidance provided is a genus of compounds, which are preferably *Raf-kinase* inhibitors.

The quantity of experimentation needed to make or use the invention

- (a) It is not known which of the unrepresented compounds meet the structural requirements for activity. Thus, one of ordinary skill would not be enabled by the disclosure to make/use the claimed kinase inhibitors. The amount of experimentation needed to practice the invention is deemed to be undue. Further, absent a utility alternate to kinase inhibition, one of ordinary skill would not be enabled to use the compounds within the genus that are not adequately supported.
- (b) In view of the low level of predictability, one of ordinary skill is not enabled by the instant disclosure to practice the invention commensurate in scope with the claims – ie. inhibition of the entirety of the enzymes classified as “kinases” with the instantly claimed genus of compounds.

Claim Rejections - 35 USC § 112 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

- 8. Claim 5 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 refers to Table 1 in the instant specification. Claims must stand alone to define the invention and incorporation by express reference to specification and/or drawings is not permitted. One must refer back to the specification to determine what Applicant is claiming by

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the express reference to the tables. It is suggested that Applicant insert the data from the appropriate tables into the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 1, 3, 6 and 9-11 rejected under 35 U.S.C. 102(e) as being anticipated by Strobel et al. (US 2004/0110808; priority date December 12, 2002). The reference teaches the compound shown in Section 3 and pharmaceutical compositions thereof.

Conclusion

10. No claims allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sun Jae Y. Loewe whose telephone number is (571) 272-9074.

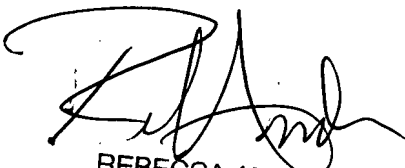
The examiner can normally be reached on M-F 7:30-5:00 Est.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sun Jae Y. Loewe
Art Unit 1626



REBECCA ANDERSON
PRIMARY EXAMINER